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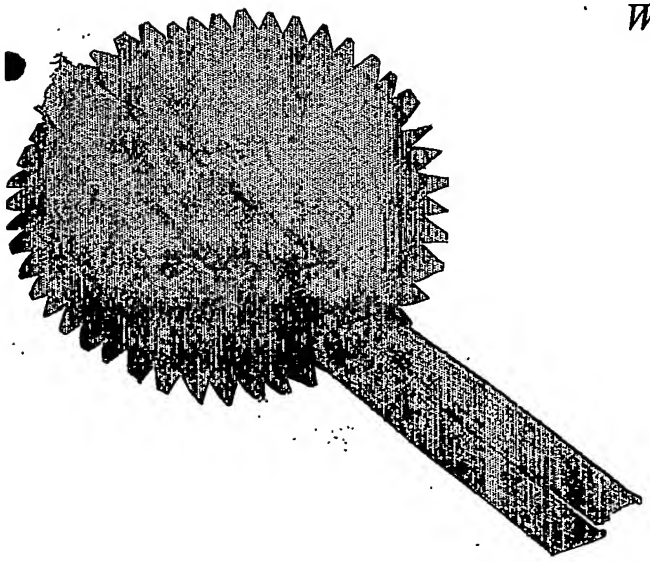
GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
W - 5, WEST PATEL NAGAR
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.**1248/Del/2003** dated **08th October 2003**.*

Witness my hand this 1st day of March 2005.



(S.K. PANGASA)
Assistant Controller of Patents & Designs

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1248-03

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT
(See Sections 5(2), 7, 54 and 135; and rule 39)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"SERTRALINE ORAL LIQUID CONCENTRATE"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. PRAVEEN RAHEJA
b. SHASHIKANTH ISLOOR
c. SANJEEV SETHI

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon.– 122001 (Haryana), India, all Indian Nationals.

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows: **NOT APPLICABLE**

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: **NOT APPLICABLE**

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on ..... Under section 16 of the Act. **NOT APPLICABLE**

7. That we are the assignee or legal representatives of the true and first inventors.

8. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana). INDIA.

9. Following declaration was given by the inventors or applicants in the convention country:

We, PRAVEEN RAHEJA, SHASHIKANTH ISLOOR, SANJEEV SETHI of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention or applicant in the convention country declare that the applicant herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a.

(PRAVEEN RAHEJA)

b.

(SHASHIKANTH ISLOOR)

c.

(SANJEEV SETHI)

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Followings are the attachment with the application:
    a. Complete Specification (3 copies)
    b. Drawings (3 copies)
    c. Priority document(s)
    d. Statement and Undertaking on FORM – 3
    e. Power of Authority (Not required)
    f. Fee Rs.**3,000/-** (Rupees Three Thousand only..) in cheque bearing No. dated : drawn on HDFC Bank Limited, New Delhi.

We request that a patent may be granted to us for the said invention.

Dated this 7TH day of **October, 2003.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM 2

The Patents Act, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

SERTRALINE ORAL LIQUID CONCENTRATE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

Technical Field of the Invention

The present invention relates to an oral liquid pharmaceutical composition comprising sertraline and pharmaceutically acceptable salts thereof. It also relates to a process for the preparation thereof.

Background of the invention

Sertraline is a selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of depression, obsessive-compulsive disorder, post-traumatic stress disorder and panic disorder. Chemically, it is (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-nanphthalenamine. It is sold under the brand name Zoloft® as tablets and capsules in the strengths of 25mg, 50mg and 100mg.

Although, the tablets and capsule dosage forms are a convenient mode of administering a required dose, but in certain cases it is not preferable to use these dosage forms such as in case of children and elderly patients who have difficulty in swallowing. Patient compliance is reduced in these cases and a successful completion of long term therapy is not possible. A liquid dosage form of sertraline is desirable which is easy to take and thus would improve patient compliance.

US Patent Application No. 2003/0096868 discloses an essentially non-aqueous liquid concentrate of sertraline comprising sertraline or its salts dissolved in a non-aqueous vehicle such as alcohol and glycerine. The concentrate is diluted with a predetermined quantity of aqueous vehicle prior to dosing. The use of non-aqueous vehicles like alcohol and glycerine, particularly alcohol needs to be minimized if not avoided as it might be unacceptable to some patients. Moreover, the use of these non-aqueous vehicles require additional settings in the manufacturing setup due to environmental considerations. Also, it is not economical to use these non-aqueous vehicles.

We have now surprisingly discovered that pharmaceutical compositions of sertraline having more than 10% water can be easily prepared. The quantity of non-aqueous solvents is reduced and is thus environment friendly as well as economical. The oral

liquid compositions are palatable with acceptable taste, can be easily swallowed and thus improving patient compliance.

Summary of the invention

In one general aspect, it relates to a pharmaceutical composition in the form of an oral liquid concentrate comprising sertraline or a pharmaceutically acceptable salt and water wherein water is more than 10% w/w of the composition to about 40% w/w of the composition.

In another general aspect, it relates to a pharmaceutical composition in the form of an oral liquid concentrate comprising sertraline or a pharmaceutically acceptable salt, one or more non-aqueous vehicle(s) and water wherein water is more than 10% w/w of the composition to about 40% w/w of the composition.

In another general aspect it relates to a pharmaceutical composition in the form of an oral liquid concentrate comprising sertraline or a pharmaceutically acceptable salt, one or more non-aqueous vehicle(s) and water wherein water is more than 10% w/w of the composition to about 40% w/w of the composition and wherein the composition is free of polyethylene glycol.

In another general aspect, it relates to a method of using a pharmaceutical composition in the form of an oral liquid concentrate wherein the method comprises diluting the oral liquid concentrate with an aqueous vehicle and administering to the patient in need thereof, wherein the oral liquid concentrate comprises sertraline or pharmaceutically acceptable salt thereof and water wherein water is more than 10% w/w of the composition to about 40% w/w of the composition.

In another general aspect, it relates to a method of treating or preventing depression, obsessive compulsive disorder, panic disorder and post-traumatic stress disorder wherein the method comprises diluting a pharmaceutical composition in the form of an oral liquid concentrate with an aqueous vehicle and administering to the patient in need thereof wherein the oral liquid concentrate comprises sertraline or a pharmaceutically

acceptable salt thereof and water wherein water is more than 10% w/w of the composition to about 40% w/w of the composition.

In another general aspect, it relates to a method of treating or preventing depression, obsessive compulsive disorder, panic disorder and post-traumatic stress disorder wherein the method comprises diluting a pharmaceutical composition in the form of an oral liquid concentrate with an aqueous vehicle and administering to the patient in need thereof wherein the oral liquid concentrate comprises sertraline or a pharmaceutically acceptable salt thereof and water wherein water is more than 10% w/w of the composition to about 40% and wherein the composition is free of polyethylene glycol.

In another general aspect, it relates to a process for the preparation of a pharmaceutical composition in the form of an oral liquid concentrate comprising sertraline or pharmaceutically acceptable salt, one or more non-aqueous vehicles(s) and water wherein the process comprises dissolving sertraline or pharmaceutically acceptable salt in non-aqueous vehicle or mixture of non aqueous vehicle and water and wherein the water is more than 10% w/w of the composition to about 40% w/w of the composition.

In another general aspect, it relates to a process for the preparation of a pharmaceutical composition in the form of an oral liquid concentrate comprising sertraline or pharmaceutically acceptable salt, one or more non-aqueous vehicles(s) and water wherein the process comprises dissolving sertraline or pharmaceutically acceptable salt in non-aqueous vehicle or mixture of non aqueous vehicle and water and wherein the water is more than 10% w/w of the composition to about 40% w/w of the composition and wherein the composition is free of polyethylene glycol.

Detailed description of the invention

The term "oral liquid concentrate" as used herein is a strong solution comprising sertraline or pharmaceutically acceptable salt, which is to be diluted with an aqueous vehicle prior to dosing.

Sertraline or a pharmaceutically acceptable salt include sertraline free base and its hydrochloride or mesylate salt or any other salt that may be used to prepare

pharmaceutical composition according to the invention. Particularly suitable is sertraline hydrochloride salt. Sertraline may comprise from about 0.1 mg/mL to about 70mg/mL, particularly from about 15mg/mL to about 30 mg/mL and more particularly the suitable concentration is about 20mg/mL, which is equivalent to about 22.4mg/mL of the hydrochloride salt.

Water as used herein may be distilled water, purified water or deionised water. The water may be present in an amount of more than 10% to about 40% w/w of the composition. Particularly, it can be upto about 25%, more particularly, it can be upto about 15% w/w of the composition.

One or more non-aqueous vehicle may be any non-toxic solvent, which can solubilize sertraline and also is suitable for human consumption such as ethanol, glycerine and propylene glycol. The use of polyethylene glycol has been exemplified in US 2003/0096868. However, we have found out that liquid PEGs are incompatible with sertraline hydrochloride and immediately result in discoloration when in physical contact and hence should be avoided. Particularly suitable are ethanol and glycerine. Ethanol may be present in the concentration of upto about 70%, particularly about 50%, more particularly upto about 30% w/w of the composition. Ethanol may be anhydrous ethanol or any suitable grade such as distilled ethanol. Glycerine may be present in an amount of upto about 90% w/w of the composition. Particularly, glycerin may be present in an amount of upto about 80%, more particularly upto about 75%, w/w of the composition.

The oral liquid concentrate may further comprise preservatives and flavouring agents.

The preservatives may include antioxidants, metal chelators, metal complexing agents and antimicrobial agents or a combination thereof. Examples include, but not limited to, butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate, ascorbic acid, ascorbyl palmitate, sodium metabisulite, sodium bisulfite, sodium thiosulfate, sodium hydroxide, cystiene, ethylenediamine tetraacetic acid or its salts (such as the sodium salt), citric acid, triethanolamine, thioglycerol, methyl paraben and propyl paraben. Particularly suitable is butylated hydroxytoluene. The preservative may be present in an amount of about 0.01 to about 10 mg/mL, particularly from about 0.1 to about 5 mg/mL.

The flavouring agents may include menthol, peppermint, spearmint, citrus, strawberry, raspberry, flavour blackcurrant, orange and grape fruit flavours. Sweeteners like aspartame and saccharin sodium can also be added as flavouring agents.

The oral concentrate as used herein is intended to dilution prior to administration. The dilution can be done with a suitable aqueous vehicle, for example, water, orange juice, ginger ale, lemon lime soda, lemonade, crane berry juice, grape fruit juice, tomato juice, pineapple juice and prune juice. The dilution may be done according to the dose required i.e. the concentrate can be diluted with a sufficient quantity of aqueous vehicle to provide a dose of sertraline such as about 25 mg and 50mg of sertraline.

The process of preparing the oral liquid concentrate involves simple manufacturing steps and conventional equipments. The process comprises dissolving sertraline or a pharmaceutically acceptable salt in a non-aqueous vehicle and adding water or dissolving sertraline in a mixture of non-aqueous vehicle and water and optionally adding flavouring agents and preservatives to the above solution; filtering the solution and filling in suitable containers.

In one embodiment, the oral liquid concentrate is prepared by dissolving sertraline hydrochloride in a mixture of ethanol and a part of glycerine with stirring, adding remaining part of glycerine and water with stirring to the above solution; filtering and filling the solution into a suitable container.

In another embodiment, the oral liquid concentrate is prepared by dissolving sertraline hydrochloride in glycerine with stirring; adding water to the above solution with stirring, filtering and filling the solution into a suitable container.

In yet another embodiment, the oral liquid concentrate is prepared by dissolving sertraline hydrochloride in propylene glycol with stirring, adding water to the above solution with stirring; filtering and filling the solution into a suitable container.

In still another embodiment, the oral liquid concentrate is prepared by dissolving sertraline hydrochloride in a mixture of ethanol and a part of propylene glycol with stirring, adding remaining quantity of propylene glycol and water with stirring to the above solution; filtering and filling the solution into a suitable container.

In another embodiment, the oral liquid concentrate is prepared by dissolving sertraline hydrochloride in propylene glycol with stirring, adding glycerine and water with stirring to the above solution; filtering and filling the solution into a suitable container.

The following examples are intended to illustrate the invention and not to be construed as limiting the scope of the invention in any way.

EXAMPLE 1

Ingredient	Quantity (mg/mL)
Sertraline hydrochloride (eq. to 20 mg of sertraline)	22.36
Ethanol 99.9%	151
Menthol	0.5
Butylated hydroxytoluene	0.1
Glycerine	q.s.
Purified Water	177.75
Total	**1000 ml**

Procedure

1. Butylated hydroxytoluene and menthol were dissolved in a portion of ethanol under stirring.
2. Sertraline was dissolved in glycerine and remaining quantity of ethanol and added to the solution of step (1) solution under stirring.
3. Purified water added to the above solution of step (2) with stirring.
4. The final volume was made up with glycerine.
5. The above solution was filtered and packed in suitable container.

EXAMPLE 2

Ingredient	Quantity (mg/mL)
Sertraline hydrochloride (eq. to 20 mg of sertraline)	22.36
Menthol	0.5
Ethanol 99.9%	151
Butylated Hydroxytoluene	0.1
Propylene glycol	q.s.
Purified Water	177.75
Total	**1000ml**

Procedure

1. Menthol and butylated hydroxytoluene were dissolved in a portion of ethanol under stirring.
2. Propylene glycol and remaining quantity of ethanol were added to the solution of step (1) under stirring.
3. Sertraline was added to the above solution under stirring.
4. Purified water was added to the solution of step (3) under stirring.
5. The final volume was made up with propylene glycol.
6. The above solution was filtered and packed in suitable container.

EXAMPLE 3

Ingredient	Quantity (mg/mL)
Sertraline hydrochloride (eq. to 20 mg of sertraline)	22.36
Menthol	0.5
Butylated Hydroxy Anisole	0.1
Propylene Glycol	q.s.
Purified water	177.75
Total	**1000 ml**

Procedure

1. Menthol and butylated hydroxy Anisole were dissolved in a portion of propylene glycol under stirring.
2. Sertraline was added to the solution of step (1) under stirring and purified water added.
3. The final volume was made up with propylene glycol.
4. The above solution was filtered and packed in suitable container.

WE CLAIM:

1. A pharmaceutical composition in the form of an oral liquid concentrate comprising sertraline or a pharmaceutically acceptable salt and water wherein water is more than 10% w/w of the composition to about 40% w/w of the composition.
2. The composition according to claim 1 wherein the water is more than 10% w/w of the composition to about 25% w/w of the composition.
3. The composition according to claim 2 wherein the water is more than 10% w/w of the composition to about 15% w/w of the composition.
4. The composition according to claim 1 wherein the composition further comprises one or more non-aqueous vehicle, preservative and flavouring agent.
5. The composition according to claim 1 wherein the pharmaceutically acceptable salt is sertraline hydrochloride.
6. The composition according to claim 1 wherein sertraline hydrochloride is present in an amount of about 0.1 mg to about 70 mg/mL.
7. The composition according to claim 6 wherein sertraline hydrochloride is present in an amount of about 15mg/mL to about 30mg/mL.
8. The composition according to claim 4 wherein the non-aqueous vehicle is selected from the group consisting of ethanol, glycerine, propylene glycol or mixtures thereof.
9. The composition according to claim 8 wherein the non-aqueous vehicle is ethanol.
10. The composition according to claim 8 wherein the non-aqueous vehicle is glycerine.

11. The composition according to claim 8 wherein the non-aqueous vehicle is mixture of ethanol and glycerine.

12. The composition according to claim 4 wherein the preservative is selected from the group consisting of butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate, ascorbic acid, ascorbyl palmitate, sodium metabisulite, sodium bisulfite, sodium thiosulfate, sodium hydroxide, cystiene, ethylenediamine tetraacetic acid or its salts, citric acid, triethanolamine, thioglycerol, methyl paraben and propyl paraben.

13. The composition according to claim 12 wherein the preservative is butylated hydroxytoluene.

14. The composition according to claim 4 wherein the flavouring agent is selected from the group consisting of menthol, peppermint, spearmint, citrus, strawberry, raspberry, flavour blackcurrant, orange and grape fruit flavours, aspartame and saccharin sodium.

15. A pharmaceutical composition the form of an oral liquid concentrate comprising sertraline or a pharmaceutically acceptable salt and water wherein water is more than 10% w/w of the composition to about 40% w/w of the composition and wherein the composition is free of polyethylene glycol.

16. The pharmaceutical composition according to claim 15 wherein water is more than 10% of the composition to about 40%w/w of the composition.

17. The pharmaceutical composition according to claim 16 wherein water is more than 10% w/w of the composition to about 25% w/w of the composition.

18. A process for the preparation of a pharmaceutical composition in the form of an oral liquid concentrate comprising sertraline or pharmaceutically acceptable salt, one or more non-aqueous vehicles(s) and water wherein the process comprises dissolving sertraline or pharmaceutically acceptable salt

in non-aqueous vehicle or mixture of non aqueous vehicle and water and wherein the water is more than 10% w/w of the composition to about 40% w/w of the composition.

19. The process according to claim 18 wherein water is more than 10%w/w of the composition to about 25% w/w of the composition.

20. The process according to claim 19 wherein water is more than 10% w/w of the composition to about 15% w/w of the composition.

21. The process according to claim 18 wherein the pharmaceutically acceptable salt is sertraline hydrochloride.

22. The process according to claim 21 wherein sertraline hydrochloride is present in an amount of about 0.1 mg to about 70 mg/mL.

23. The process according to claim 22 wherein sertraline hydrochloride is present in an amount of about 15mg/mL to about 30mg/mL.

24. The process according to claim 18 wherein the non-aqueous vehicle is selected from the group consisting of ethanol, glycerine, propylene glycol or mixture thereof.

25. The process according to claim 24 wherein the non-aqueous vehicle is ethanol.

26. The process according to claim 24 wherein the non-aqueous vehicle is glycerine.

27. The process according to claim 24 wherein the non-aqueous vehicle is mixture of ethanol or glycerine.

28. The process according to claim 18 wherein the process further comprises adding a preservative or a flavouring agent.

29. The process according to claim 28 wherein the preservative is selected from the group consisting of butylated hydroxytoluene, butylated hydroxyanisole,

propyl gallate, ascorbic acid, ascorbyl palmitate, sodium metabisulite, sodium bisulfite, sodium thiosulfate, sodium hydroxide, cystiene, ethylenediamine tetraacetic acid or its salts, citric acid, triethanolamine, thioglycerol, methyl paraben and propyl paraben.

30. The process according to claim 29 wherein the preservative is butylated hydroxytoluene.

31. The process according to claim 28 wherein the flavouring agent is selected from the group consisting of menthol, peppermint, spearmint, citrus, strawberry, raspberry, flavour blackcurrant, orange and grape fruit flavours, aspartame and saccharin sodium.

32. A method of using a pharmaceutical composition in the form of an oral liquid concentrate wherein the method comprises diluting the oral liquid concentrate with an aqueous vehicle and administering to the patient in need thereof, wherein the oral liquid concentrate comprises sertraline or pharmaceutically acceptable salt thereof and water wherein water is more than 10% w/w of the composition to about 40% w/w of the composition.

33. A method of treating or preventing depression, obsessive compulsive disorder, panic disorder and post-traumatic stress disorder wherein the method comprises diluting a pharmaceutical composition in the form of an oral liquid concentrate with an aqueous vehicle and administering to the patient in need thereof wherein the oral liquid concentrate comprises sertraline or a pharmaceutically acceptable salt thereof and water wherein water comprises more than 10% w/w of the composition to about 40% w/w of the composition.

34. The method according to claims 32 or 33 wherein the aqueous vehicle is selected from the group consisting of water, orange juice, ginger ale, lemon lime soda, lemonade, crane berry juice, grape fruit juice, tomato juice, pineapple juice and prune juice.

Dated this 7TH day of **October, 2003.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

ABSTRACT

SERTRALINE ORAL LIQUID CONCENTRATE

The present invention relates to an oral liquid pharmaceutical composition comprising sertraline and pharmaceutically acceptable salts thereof. It also relates to a process for the preparation thereof.